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EXAMINER	
NGUYEN, QUANG	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 08/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/075,322	CURIEL ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-7 and 10-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4-7 and 10-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed on 4/27/06 was entered, even though technically it does not comply with the requirements of 37 CFR 1.121(c) because the space between the terms "modification" and "comprising" on line 4 of amended claim 1 is underlined. However, for the purpose of a compact prosecution and due to such a minor non-compliance, the amendment was entered.

Amended claims 1, 4-7 and 10-12 are pending in the present application, and they are examined on the merits herein.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 4-6 and 10-12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the same reasons already set forth in the Office Action mailed on 7/28/04 (pages 4-6). **The rejection is reinstated below, and therefore it constitutes a new ground of rejection.**

The claims are drawn to a transductionally and transcriptionally modified adenoviral vector comprising a targeting component that targets the vector to specific

target cells, wherein the targeting component comprises a bi-specific antibody conjugate linking the Fab fragment of an anti-Ad5 knob antibody 1D6.14 with the anti-angiotensin converting enzyme antibody 9B9, and a tissue specific promoter that drives the expression of a transgene carried by said vector in said target cells, wherein an angiotensin converting enzyme is expressed on the target cells, and a method of increasing targeting specificity to target cells and reducing transgene expression in non-target cells using the same adenoviral vector.

The application discloses the transductionally and transcriptionally modified adenoviral vector comprising a targeting component comprising a bi-specific antibody conjugate linking the anti-Ad5 knob antibody 1D6.14 with the anti-angiotensin converting enzyme antibody 9B9, that is encompassed by the definitions for **biological material** set forth in 37 C.F.R. § 1.801. Because it is apparent that this biological material, specifically the bi-specific antibody conjugate linking the anti-Ad5 knob antibody 1D6.14 with the anti-angiotensin converting enzyme antibody 9B9, is essential for practicing the claimed invention, it must be obtainable by a reproducible method set forth in the specification or otherwise be known and readily available to the public as detailed in 37 C.F.R. §§ 1.801 through 1.809. Particularly, the 1D6.14 antibody or its Fab fragment is recognized to have a high affinity binding to recombinant Ad5 knob and its ability to neutralize Ad5 infection of HeLa cells (Sosnowski et al., WO 98/40508, Cited previously, page 30, lines 14-20).

Although the anti-angiotensin converting enzyme monoclonal antibody 9B9 is apparently readily available to the public (Muzykantov et al., US 5,653,979, see abstract

and the claims), it is unclear whether the anti-Ad5 knob antibody 1D6.14 is also readily available to the public or that the written instructions are sufficient to reproducibly construct the bi-specific antibody conjugate linking 1D6.14 antibody with 9B9 antibody from starting materials known and readily available to the public. Accordingly, availability of such biological material is deemed necessary to satisfy the enablement provisions of 35 U.S.C. § 112.

If the anti-Ad5 knob antibody 1D6.14 is not obtainable or available, the requirements of 35 U.S.C. § 112 may be satisfied by a deposit of the biological material. In order for a deposit to meet all criteria set forth in 37 C.F.R. §§ 1.801-1.809, applicants or assignee must provide assurance of compliance with provisions of 37 C.F.R. §§ 1.801-1.809, in the form of a declaration or applicant's representative must provide a statement. **The content of such a declaration or statement is suggested by the enclosed attachment.** Because such deposit will not have been made prior to the effective filing date of the instant application, applicant is required to submit a verified statement from a person in a position to corroborate the fact, which states that the biological material which has been deposited is the biological material specifically identified in the application as filed (37 C.F.R. § 1.804). Such a statement need not be verified if the person is an agent or attorney registered to practice before the Office. Applicant is also reminded that the specification must contain reference to the deposit, including deposit (accession) number, date of deposit, name and address of the depository, and the complete taxonomic description.

Response to Arguments

Applicants' argument related to the above rejection in the Amendment filed on 10/11/2005 (pages 4-5) has been fully considered, but it is respectfully not found persuasive.

Applicants argue basically that the Examiner states that a deposit of the anti-Ad5 knob antibody 1D6.14 may overcome the above rejection, and Applicants have deposited 25 vials of hybridoma 1D6.14 to the ATCC patent depository on September 14, 2005.

It is noted that Applicants still have not complied fully to all of the requirements for a deposit of biological material outlined in the enclosed attachment. Accordingly, claims 4-6 and 10-12 are still rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement for the reasons set forth above.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 4-7 and 10-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sosnowski et al. (WO 98/40508; Cited previously) in view of Muzykantov et al. (Am. J. Physiol. 270: L704-L713, 1996; IDS) for the same reasons already set forth in the Office Action mailed on 10/26/05 (pages 4-7). The same rejection is restated below.

Sosnowski et al. disclose a re-targeted, tropism-modified adenoviral vector system that specifically target cells expressing a preselected receptor, comprising an antibody or fragment thereof that binds an adenoviral capsid protein (including an adenoviral knob protein); a targeting ligand that binds the preselected receptor; and an adenovirus containing a nucleic acid molecule that encodes a therapeutic gene product under the control of a promoter (including a tissue-specific promoter); wherein the ligand is conjugated to the antibody or fragment thereof and wherein the antibody or fragment thereof is bound to the adenovirus (page 4, lines 17-25; page 8, line 27 continues to line 1 of page 9). Sosnowski et al further teach that tissue specific promoters are particularly useful for expression in a wide variety of cells, including endothelial and smooth muscle cells, and by using one of this class of promoters, an extra margin of specificity can be attained (page 75, lines 3-5). Exemplary endothelial-specific promoters include VEGF-receptor promoter among others (page 75, line 17 continues

to line 19 of page 76). Sosnowski et al. further teach the utilization of bi-specific antibodies (see the section on Bi-specific Antibodies, pages 28-33, particularly page 30, lines 14-17) that recognizes an Ad knob protein (e.g., 1D6.14 antibody or its Fab fragment known for its high affinity binding to recombinant Ad5 knob and its ability to neutralize Ad5 infection of HeLa cells) as well as the target cell-specific receptor to ablate endogenous adenoviral tropism. Sosnowski et al. also teach that any antibody that recognizes a molecule internalized following binding, including but not limited to antibodies to molecules on endothelial cells such as antibodies to FGF receptors, VEGF receptors, E- and P-selectins and others (see pages 43-48).

Sosnowski et al. do not teach specifically the utilization of a bi-specific antibody conjugate linking a Fab fragment of an anti-Ad5 knob antibody with an anti-angiotensin converting enzyme antibody, more specifically a bi-specific antibody conjugate linking 1D6.14 and 9B9 antibody, in their tropism-modified adenoviral vector system.

However, at the effective filing date of the present application Muzykantov et al. already disclose that the Mab 9B9 to angiotensin converting enzyme is a safe, specific and useful carrier for drugs targeting to the pulmonary vascular endothelium after systemic administration, and that Mab 9B9 is internalized by endothelial cells both *in vitro* and *in vivo* without significant intracellular degradation (see abstract).

Accordingly, it would have been obvious for an ordinary skilled artisan in the art to modify the retargeted, tropism-modified adenoviral vector system of Sosnowski et al. by utilizing a bi-specific antibody conjugate linking a Fab fragment of an anti-Ad5 knob antibody with an anti-angiotensin converting enzyme antibody, and more specifically the

bi-specific antibody conjugate linking 1D6.14 and 9B9 antibody to target the modified adenoviral vector containing a transgene specifically to pulmonary vascular endothelium after a systemic delivery in light of the teachings of Muzykantov.

An ordinary skilled artisan would have been motivated to carry out the above modification because Muzykantov et al. already teach that Mab 9B9 is a **safe, specific** and **useful carrier for drugs targeting specifically to the pulmonary vascular endothelium after systemic administration** and that the antibody is internalized by endothelial cells both *in vitro* and *in vivo* and that it is not significantly degraded intracellularly. Moreover, Sosnowski et al. clearly teach that **any antibody that recognizes a molecule expressed on the surface of target cells can be utilized as long as the antibody is internalized following binding, including but not limited to antibodies to molecules on endothelial cells, and that 1D6.14 antibody or its Fab fragment is already known for its high affinity binding to recombinant Ad5 knob**. The modified re-targeted, tropism-modified adenoviral vector system would result in increasing targeting specificity to pulmonary vascular endothelial cells expressing angiotensin converting enzyme and reducing transgene expression in non-pulmonary vascular endothelial cells.

An ordinary skilled artisan would have a reasonable expectation of success to carry out the above modification in light of the teachings of Sosnowski et al. and Muzykantov et al., coupled with a high level of skills of an ordinary skilled artisan in the art of making modified adenoviral vectors at the effective filing date of the present application.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

Applicants' arguments related in part to the above rejection in the Amendment filed on 4/27/06 (pages 6-9) have been fully considered, but they are not found persuasive.

1. Applicants argue basically that neither Sonsnowski et al. nor Muzykantov et al. have contemplated or expressed the need to combine the two different elements, namedly an anti-Ad5 antibody and anti-angiotensin converting enzyme antibody via a bispecific antibody conjugate. Applicants further argue that based on the teachings and the successes of Sosnowki et al. and Muzynkantov et al., a person having ordinary skill in the art would not be motivated to combine these two components.

Once again, it should be noted that this is a 103 rejection, and therefore each cited reference does not have to teach every element of the claims. An ordinary skilled artisan would have been motivated to carry out the above modification because Muzykantov et al. already teach that Mab 9B9 is a **safe, specific** and **useful carrier for drugs targeting specifically to the pulmonary vascular endothelium after systemic administration** and that the antibody is internalized by endothelial cells both *in vitro* and *in vivo* and that it is not significantly degraded intracellularly. Moreover, Sosnowski et al. clearly teach that **any antibody that recognizes a molecule expressed on the surface of target cells can be utilized as long as the antibody is internalized**

following binding, including but not limited to antibodies to molecules on endothelial cells, and that 1D6.14 antibody or its Fab fragment is already known for its high affinity binding to recombinant Ad5 knob. It should be further emphasized that Sosnowski et al clearly teach **the utilization of bi-specific antibodies** (see the section on Bi-specific Antibodies, pages 28-33, particularly page 30, lines 14-17) that recognizes an Ad knob protein (e.g., 1D6.14 antibody or its Fab fragment known for its high affinity binding to recombinant Ad5 knob and its ability to neutralize Ad5 infection of HeLa cells) as well as the target cell-specific receptor to ablate endogenous adenoviral tropism. The modified re-targeted, tropism-modified adenoviral vector system would result in increasing targeting specificity to pulmonary vascular endothelial cells expressing angiotensin converting enzyme and reducing transgene expression in non-pulmonary vascular endothelial cells.

2. Applicants further argue that there is no teaching or demonstration that shows how a vector of the presently claimed invention could be constructed, and whether such a vector would be stable or would be as effective, if not more effective when delivered *in vivo*. Therefore, one would still be trying to arrive at the instant invention, and trying is not a standard of obviousness.

Once again, it should be noted that this is a 103 rejection. With respect to Applicant's doubt on the expected success of the combined teachings of Sosnowki et al. and Muzykantov et al., please refer to the successes already demonstrated by Sosnowski et al. (WO 98/40508). It is further noted that the results of Sosnowski et al. (WO 98/40508) are the same results present in U.S. Patent 6,613,563 that has claims

drawn to a tropism-modified adenoviral vector system that specifically targets cells expressing a preselected receptor, wherein the adenoviral vector contains a tissue-specific promoter operatively linked to a nucleic acid molecule that encodes a gene product, and wherein the gene product enhances cellular proliferation or cellular differentiation (see claims 1-7 of the issued U.S. Patent). Muzykantov et al. also demonstrated clearly that the Mab 9B9 to angiotensin converting enzyme is a safe, specific and useful carrier for drugs targeting to the pulmonary vascular endothelium after systemic administration. It is unclear to the examiner why the adenoviral vector resulting from the combined teachings of Sosnowki et al. and Muzykantov et al. would not be expected to be stable or would not be effective as alleged by Applicants, especially in light of the teachings of the cited references. Applicants have not provided any reasonable rationales and/or evidence to support this allegation. The above 103 rejection has established that the claimed invention as a whole was *prima facie* obvious, and therefore that this is not a trying situation as alleged by Applicants.

Accordingly, claims 1, 4-7 and 10-12 are still rejected under 35 U.S.C. 103(a) for the reasons set forth above.

Claims 1, 4-7 and 10-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reynolds et al. (Mol. Ther. 2: 562-578, 2000) in view of Sosnowski et al. (WO 98/40508; Cited previously) for the same reasons already set forth in the Office Action mailed on 10/26/05 (pages 10-12). The same rejection is restated below.

Reynolds et al disclose a targetable, injectable adenoviral vector for selective gene delivery to pulmonary endothelium *in vivo*, said vector comprises a bispecific antibody (Mab 9B9 conjugated to 1D6.14 anti-knob Fab antibody) that target Ad infection specifically to angiotensin-converting enzyme, which is preferentially expressed on pulmonary capillary endothelium (see abstract and the Methods section). Reynolds et al further teach that administration of retargeted vector complex via tail vein injection into rats resulted in at least a 20-fold increase in both Ad DNA localization and luciferase transgene expression in the lungs, compared to the untargeted vector. Additionally, targeting led to reduced transgene expression in nontarget organs, especially the liver, where the reduction was over 80%. Reynolds et al. also state that "However, further refinements to avoid nonspecific uptake of vector by the reticuloendothelial system may be required for optimal efficacy" (page 577, col. 1, bottom of second paragraph).

Reynolds et al do not specifically teach the use of any tissue specific promoter, including the vascular endothelial growth factor type I receptor promoter, in the disclosed adenoviral vector for expressing a transgene.

However, at the effective filing date of the present application Sosnowski et al. already disclose a re-targeted, tropism-modified adenoviral vector system that specifically target cells expressing a preselected receptor, comprising an antibody or fragment thereof that binds an adenoviral capsid protein (including an adenoviral knob protein); a targeting ligand that binds the preselected receptor; and an adenovirus containing a nucleic acid molecule that encodes a therapeutic gene product under the

control of a promoter (including a tissue-specific promoter); wherein the ligand is conjugated to the antibody or fragment thereof and wherein the antibody or fragment thereof is bound to the adenovirus (page 4, lines 17-25; page 8, line 27 continues to line 1 of page 9). Sosnowski et al teach specifically that tissue specific promoters are particularly useful for expression in a wide variety of cells, including endothelial and smooth muscle cells, and by using one of this class of promoters, an extra margin of specificity can be attained (page 75, lines 3-5). Exemplary endothelial-specific promoters include VEGF-receptor promoter among others (page 75, line 17 continues to line 19 of page 76).

Accordingly, it would have been obvious for an ordinary skilled artisan in the art to modify the targetable, injectable adenoviral vector system of Reynolds et al. by also incorporating the use of an endothelial cell specific promoter such as VEGF-receptor promoter in light of the teachings of Sosnowski et al.

An ordinary skilled artisan would have been motivated to carry out the above modification because Sosnowski et al already teach **the use of an endothelial cell specific promoter provides an extra margin of specificity** (page 75, lines 3-5), and that this would be a refinement that avoids the nonspecific uptake and non-specific expression of a transgene in non-targeted cells *in vivo*.

An ordinary skilled artisan would have a reasonable expectation of success to carry out the above modification in light of the teachings of Reynolds et al. and Sosnowski et al., coupled with a high level of skills of an ordinary skilled artisan in the

art of making modified adenoviral vectors at the effective filing date of the present application.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

Applicants' arguments related in part to the above rejection in the Amendment filed on 4/27/06 (pages 9-11) have been fully considered, but they are not found persuasive.

Applicants argue basically that although Reynolds et al state further refinements to avoid non-specific uptake of vector, they do not specify the refinements; and although Sosnowski et al. teach the use of tissue specific promoters for expression in endothelial and smooth muscle cells, they do not demonstrate the use of these promoters in their constructs. Therefore, although the combined teachings of the two references may motivate one of ordinary skill in the art to use such promoters in their constructs, one may still be trying to construct the vector absent teachings of the instant invention; and trying is not a standard of obviousness.

Once again, it should be noted that this is a 103 rejection, and therefore each cited reference does not have to teach every element of the claims. The examiner has provided the teachings of Reynolds et al., Sosnowski et al., motivation for the combination of these references as well as a reasonable expectation of success; and

therefore the examiner has established that the claimed invention as a whole was *prima facie* obvious. This is not the situation of trying as alleged by Applicants.

Accordingly, claims 1, 4-7 and 10-12 are still rejected under 35 U.S.C. 103(a) for the reasons set forth above.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's SPE, Dave Nguyen, may be reached at (571) 272-0731.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

QUANG NGUYEN, PH.D
PATENT EXAMINER

SUGGESTION FOR DEPOSIT OF BIOLOGICAL MATERIAL

A declaration by applicant or assignee, or a statement by applicant's agent identifying a deposit of biological material and averring the following may be sufficient to overcome an objection or rejection based on a lack of availability of biological material. Such a declaration:

1. Identifies declarant.

2. States that a deposit of the material has been made in a depository affording permanence of the deposit and ready accessibility thereto by the public if a patent is granted. The depository is to be identified by name and address. (See 37 C.F.R. § 1.803).

3. States that the deposited material has been accorded a specific (recited) accession number.

4. States that all restrictions on the availability to the public of the material so deposited will be irrevocably removed upon the granting of the patent. (See 37 C.F.R. § 1.808(a)(2)).

5. States that the material has been deposited under conditions that assure that access to the material will be available during the pendency of the patent application to one determined by the Commissioner to be entitled thereto under 37 C.F.R. § 1.14 and 35 U.S.C. § 122. (See 37 C.F.R. § 1.808(a)(1)).

6. States that the deposited material will be maintained with all the care necessary to keep it viable and uncontaminated for a period of at least five years after the most recent request for the furnishing of a sample of the deposited microorganism, and in any case, for a period of at least thirty (30) years after the date of deposit or for the enforceable life of the patent, whichever period is longer. See 37 C.F.R. § 1.806).

7. That he/she declares further that all statements made therein of his/her own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the instant patent application or any patent issuing thereon.

Alternatively, it may be averred that deposited material has been accepted for deposit under the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure (e.g., see 961 OG 21, 1977) and that all restrictions on the availability to the public of the material so deposited will be irrevocably removed upon the granting of a patent.

Additionally, the deposit must be referred to in the body of the specification and be identified by deposit (accession) number, date of deposit, name and address of the depository, and the complete taxonomic description.